REMARKS

Claims 1-4, 6, and 8-14 are pending in this application. Claims 5 and 7 have been cancelled without prejudice or disclaimer. Claims 6 and 8-14 have been withdrawn by the examiner. None of the claims are amended, however, applicants provide clean copies of the pending claims for the convenience of the examiner. The Office Action is discussed below:

On pages 2-8 of the Office Action, the examiner has maintained the rejection of claims 1-4 allegedly as being unpatentable over Hille *et al.* (US patent 5,705,186) in view of Gao *et al.* (US patent publication 2003/0050257) and Remington (*The Science and Practice of Pharmacy.* 20th edition, published 2000 by Lippincott Williams and Wilkins, pp. 704-712).

On pages 8-13 of the Office Action, the examiner has maintained the rejection of claims 1-4 allegedly as being unpatentable over Hille *et al.* in view of Merrill *et al.* (US patent 5,593,695) and Remington.

On pages 13-18 of the Office Action, the examiner has maintained the rejection of claims 1-4 allegedly as being unpatentable over Hille *et al.* in view of Berge *et al.* and Remington.

Applicants respectfully disagree with the examiner and submit that:

> "MERE STATEMENT THAT THE CLAIMED INVENTION IS WITHIN THE CAPABILITIES OF ONE OF ORDINARY SKILL IN THE ART IS NOT SUFFICIENT BY ITSELF TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS
>
> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)."

See MPEP § 2143.01 (IV) at 2100-140 (Rev. 6, September 2007).

> When claims are directed to molecules, the inquiry turns to similarities and differences between the claimed molecule and those of the prior art. In basing obviousness on the availability of substitutions, *KSR v. Teleflex* presupposes that the art gives reasons to make a modification. However, where the art is unpredictable, such as in the biotechnology and chemical arts, *KSR*'s focus on "identifiable, predictable solutions" present a difficult hurdle for the examiner because an alleged potential solution based upon the prior art is not likely to be genuinely predictable. *Eisai Co. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452, 1456-57 (Fed. Cir. 2008).

The examiner admits that Hille *et al.* does not disclose a hydrobromide salt of morphine-6- glucuronide.

According to the examiner, Gao *et al.* discloses a number of glycosylated morphine derivatives, including 6- glucuronide adducts (refers to p. 1, paragraphs 0014-0021 that describes 3-O-glucosylhydromorphine, 3-O-glucosyldihydroisomorphine, 6-O-glucosyldihydroisomorphine, 3-O-glucosyldihydromorphine, 6-O-glucosyldihydromorphine, nordihydromorphine-3-glucuronide, nordihydroisomorphine-3-glucuronide, and norhydromorphone-3-glucuronide). However, the examiner could not provide any disclosure of the claimed hydrobromide salt of morphine-6-β-D-glucuronide (M6G.HBr) in Gao *et al.*

On page 8 of the Office Action the examiner asserts that Merrill *et al.* discloses a pharmaceutical composition comprising morphine (refers to column 1, lines 35-47), which maybe modified to a hydrobromide salt form (refers to column 1, line 58). However, the examiner could not provide any disclosure of the claimed M6G.HBr in Merrill *et al.*

The examiner relies on Berge *et al.* that discloses a number of commercially marketed pharmaceutically acceptable salts (refers to page 2, table I), including hydrobromide salt.

The examiner also relies on Remington that discloses a general drug discovery process, which employs different salts (refers to page 704, left column, second paragraph, right column, first and second paragraphs), including hydrobromide.

Based on the above references, the examiner opines that it would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion.

Applicants refer to above that mere statement that the claimed invention is within the capabilities of one ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. The examiner has not addressed why one of ordinary skill in the art would be motivated to modify morphine molecule to produce a hydrobromide salt of morphine-6-β-D-glucuronide, the claimed compound, where the art is unpredictable, such as in the biotechnology and chemical arts, that there is no reasonable expectation of success of obtaining compound with superior stability.

The examiner also has not addressed the claimed invention provides M6G.HBr, which is unexpectedly advantageous and possesses superior stability properties compared to M6G base and other M6G salts. The present application clearly demonstrates the increased stability of M6G.HBr compared with M6G.HCl (see specification, Examples 1 and 3, and Tables 1-4, for example). M6G.HBr also was found to be stable when subject to storage conditions of 25°C/60%RH and 40°C/75%RH for 3 months and 60°C for 1 month. M6G.HBr shows a very limited amount of degradation and no discoloration after storage at room temperature for six years.

There is no disclosure in the cited documents of the suitability of any of the salts for combination with M6G, nor that any particular salt forms compounds with improved stability. The examiner considers on the basis of the pKa and ClogP in Table 2 of Remington that hydrobromide is disclosed by this document to be a pharmaceutically acceptable counter ion similar to hydrochloride. On this basis, the skilled person would have no motivation to substitute the hydrochloride salt with the hydrobromide salt because they would not expect that the hydrobromide salt would provide any advantageous properties compared with the hydrochloride salt, *per se*.

Applicants reiterate, to the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on "identifiable, predictable solutions" present a difficult hurdle

for the examiner because an alleged potential solution based upon the prior art is not likely to be genuinely predictable. *See Eisai Co. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452, 1457 (Fed. Cir. 2008).

Applicants elaborate, a *prima facie* case of obviousness for chemical compound generally begins with identification of known or "lead" compound that is modified in particular way to achieve claimed compound; in the case of *Eisai Co. v. Dr. Reddy's Laboratories Ltd.*, the court ruled that the claimed rabeprazole compounds having anti-ulcerative activity would not have been rendered obvious by a prior patent disclosing ulcer treatment compound lansoprazole in combination with two other references. Lansoprazole is structurally identical to rabeprazole apart from trifluoroethoxy substituent, rather than methoxypropoxy substituent, at 4-position on pyridine ring, and this difference lends lansoprazole desired properties which would not have been apparent to this skilled person. *See Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008)

Likewise, in the instant case, the examiner cannot base a rejection on an unsupported assertion. In other words, there is no reason presented by the examiner why a skilled artisan would have considered modification of morphine-6-glucuronide to a hydrobromide salt of morphine-6-β-D-glucuronide as an identifiable, predictable solution to achieve an unexpectedly advantageous and superior stability of morphine-6-β-D-glucuronide. *See Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452, 1456-1457, (Fed. Cir. 2008)

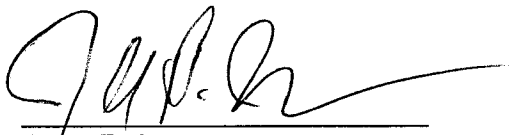
Applicants reiterate, none of the cited documents teaches or suggests that the hydrobromide salt of morphine-6-β-D-glucuronide would have advantageous properties, in particular, increased long term stability compared with morphine-6-glucuronide base and other morphine-6-glucuronide salts (including the hydrochloride salt). Further, a mere disclosure in the art that the hydrobromide ion is a pharmaceutically acceptable counter ion, as relied upon by the examiner, does not render the claimed invention obvious.

In view of the above, applicants submit that a *prima facie* case of obviousness has not been established by the examiner, accordingly, withdrawal of the obviousness rejection is solicited.

REQUEST

Applicants submit that claims 1-4 are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 416-6800 should there be any questions.

Respectfully submitted,



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